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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/903,520	07/11/2001	Avi Ashkenazi	10466/83	1093

35489 7590 02/22/2007

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/903,520	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39-47 and 49-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47 and 49-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 10/30/06 has been entered.

2. IDS filed 10/30/06 has been entered and considered. The following references were cited by Applicant in the response filed 10/25/04 but were never cited on an IDS. Since the references have been considered by examiner in this and previous Office Actions they are officially made of record and recorded on the attached PTO-892 form.

u. Thurner et al. J. Exp. Med. 190(11): 1669-1678, 1999.

v. Steinman et al. Drug News Perspect. 13(10): 581-586, 2000.

w. Gubler et al. PNAS 88: 4143-4147, 1991.

x. Peterson et al. J. Clin. Oncol. 21(12): 2342-2348, 2003.

3. Claims 1-38 and 48 are cancelled. Claims 39-47 and 49-51 are pending.

Claim Rejections Under 35 USC § 101 and 35 USC § 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 39-47 and 49-51 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility. The claims are directed to the polypeptides of SEQ ID NO:290 and variants thereof, referred to in the specification as PRO335.

The instant specification discloses that the claimed protein (PRO335, SEQ ID NO:290) tested positive in the MLR assay wherein "positive increases over control are considered positive" It was previously asserted by the Examiner that insufficient evidence was provided to support the position that the MLR assay was an art recognized *in vitro* assay that was predictive of general immune responses *in vivo*. Several references have been cited during the prosecution of the instant application which demonstrates either a showing that the results of the MLR assay are consistent *with in vivo* activity or are inconsistent with in vivo activity. Applicants argue the results of the MLR assay is valuable for identifying immune suppressive molecules *in vitro* and the results obtained from theses assays are generally predictive for their *in vivo* effectiveness. Applicants argue that U.S. patent 5,817,306 states "The mixed lymphocyte response (MLR) and phytohemagglutinin A (PHA) assays are valuable for identifying immune suppressive molecules in vitro that are useful for treating graft versus host disease. The results obtained from these assays are generally predictive of their in vivo effectiveness." (See column 12, lines 36- 41 of U.S. Pat. No. 5,817,306). Therefore, it is conceded by the Examiner that the MLR assay is art recognized for identifying molecules which suppress an immune response. It would also be likely that the assay would be useful for identifying molecules which stimulate an immune response. **However, the instant specification does not support a utility for the claimed invention for the asserted use of enhancing the immune response in an individual based on the results of the MLR assay in Example 74 disclosed in instant specification.** Assay 74 states, "Positive increases over control are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein." The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that certain proteins tested positive and the statement that "any value greater than control indicates a stimulatory effect for the test protein".

If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth regarding the nature of the MLR assay and how those skilled in the art use this assay and what kind of determinations can be made about compounds which are tested in this assay. The MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed protein The art recognizes several controls as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities (Basic & Clinical Immunology, page 246). Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-1gG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion of the specification. The specification states that "positive increases over control are considered positive", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because one of ordinary skill in the art would not conclude that a molecule

which tested positive in the assay of the specification wherein "positive increases over control are considered positive" would be useful as a molecule for therapeutically enhancing an immune response in an individual (asserted use). There is insufficient data presented, as well as insufficient controls used, to conclude anything regarding the ability of the claimed invention to be used in a substantial way to therapeutically enhance the immune response of an individual, and further experimentation would be required to use the invention in this manner.

The Declaration of Dr. Sherman Fong concludes "a PRO polypeptide shown to stimulate T- cell proliferation in the MLR assay of the present invention with an activity at least 180% of the control, as specified in the present application, is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant". In assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, and the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not the disclosure that PRO335 tested "positive" in the MLR assay of Example 74 supports the assertion that it could be used to stimulate proliferation of T-lymphocytes and therefore, be used for therapeutic enhancement of the immune system. Dr. Fong's statement that the present invention has an activity of at least 180% is questioned because there is no data presented to support this conclusion. The specification may state that increases of greater than or equal to 180% are preferred, but there is no disclosure, in the specification or in any other source, that the alleged increase reported in the specification for the claimed protein was of any particular degree. The only conclusion that can be made from the evidence provided for the claimed protein of PRO 335 is that the increase was a value greater than control since this was the standard provided for determination of a positive increase. The significance of this conclusion

can be questioned since proper assay controls, deemed essential in the art, were not used and because the standard for determination of a positive response in the assay would not be accepted by those of skill in the art (statistical significance is the standard for evaluating therapeutic value of a compound). The expert has interest in the outcome of the case since Dr. Fong is listed as an inventor and is employed by the assignee. Finally, the expert refers to Gubler et al. as factual support for the conclusions in the declaration. However, Gubler et al. do not appear to indicate that a protein shown to stimulate T-cell proliferation in an MLR assay with an activity of at least 180% would be expected to have the type of activity as that exhibited by IL-12. Further, Gubler et al. (as well as Peterson et al. and Thurner et al., all references provided by applicants on 10/25/04) are silent to any activity possessed by the claimed protein. The Fong declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility.

The PRO335 protein has not been shown to therapeutically enhance the immune system. The specification merely demonstrates that the PRO335 protein increases T-cell proliferation above control. It is not known whether this increase is significant or what the relative increase in proliferation is. In the absence of any of the above information, all that the specification does is present evidence that the PRO335 protein may increase T-cell proliferation and invites the artisan to determine the significance of this increase and whether it is meaningful (i.e. useful for a therapeutic benefit). It remains that the specification is not sufficient to conclude anything about the nature of the activity of the PRO335 protein. Based on consideration of the evidence as a whole, the finding of lack of utility based on the MLR assay of Example 74 is proper.

Appellant argues that the standard for utility is that it is "more likely than not" that the asserted utility is specific and substantial and that the Examiner has misinterpreted the focus of the assay disclosed in the specification. Appellant's argument has been fully considered, but is not persuasive. The question of whether the art recognizes the MLR assay as predictive of *in vivo* therapeutic value has been answered. However, the specification does not support the conclusion that the claimed protein (PRO335) that stimulates proliferation of T-lymphocytes such that it would have therapeutic application

for enhancing the immune response. As pointed out previously, no data is presented and the statement that proliferation was greater than control is not sufficient for concluding that the claimed protein would be useful for a therapeutic application, which is the asserted utility based on this assay. The assay relied upon in the instant specification is deficient in that proper art-recognized controls are not present, measured values of stimulation are not present, variability is not disclosed, statistical significance is not disclosed, such that an independent evaluation and conclusion cannot be made. One skilled in the art would have to do further research to determine whether or not the increase in T-cell proliferation by the PRO335 polypeptide in the MLR assay is real and significant, and therefore, support the asserted use for therapeutic enhancement of immune response. Such further research requirements make it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Appellant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in Brenner v. Manson, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

In the instant situation, further research would be required to reasonably confirm that the PRO335 stimulates T-cell proliferation to a degree that it would be useful therapeutically for stimulating an immune response, which is the asserted utility in the specification. Applicants argue a positive result for PRO335 in the MLR assay, described in Example 74, demonstrates that PRO335 is active as a stimulator of the proliferation of stimulated T-lymphocytes. Applicants' assertion is noted, but the facts of record and the disclosure of the specification do not support this conclusion. As pointed out previously, the specification indicates that "positive increases over control are considered positive", yet art recognized controls, which are considered to be necessary for determining a meaningful result, are not present. The specification fails to

include any values which were obtained from the assay, so the results of the assay cannot be independently evaluated. If the degree of stimulation is greater than the control, but within the variability of the assay, then one of ordinary skill in the art would not conclude that the protein tested is a stimulator of T-cell proliferation, yet the specification would arrive at this conclusion. In order to be useful in the manner asserted in the specification (i.e. therapeutic enhancement of an immune response), the degree of stimulation of T-cell proliferation must be meaningful. One of ordinary skill in the art would usually evaluate this by observing a statistically significant increase in T-cell proliferation over baseline. However, based on the limited disclosure in the instant specification, no conclusions can be made as to the activity of the claimed protein in this assay because proper controls are not provided and there is no data presented to evaluate. Therefore, further research would be required to reasonably confirm the asserted utility based on the MLR assay of Example 74.

Applicants' statements and arguments directed to use of the MLR to evaluate compounds for use as immunomodulators is noted. However, in view of the Examiner's concession that the MLR is an art-accepted assay for this purpose, these arguments are moot. Applicants assert that the specification clearly discloses that PRO335 tested positive in the MLR assay and that the Fong Declaration reinforces the teachings of the specification that a PRO335 polypeptide with an activity in the MLR assay of at least 180% of the control is expected to have the type of activity exhibited by IL-12, and would therefore find practical utility as an immune stimulant. First, the statement that PRO335 tested positive in the MLR assay is addressed above. The standard set forth in the specification that "positive increases over control are considered positive" is neither art accepted nor indicative of a meaningful increase in T-cell proliferation. Lacking proper controls and no data, the observation that PRO335 tested "positive" is meaningless. All assays have variability and the observed increase over control may be natural variation in the assay, and therefore, not an indication of an immunostimulatory effect. Secondly, there is no disclosure that the PRO335 protein of the instant invention has an activity in the MLR assay of at least 180%, therefore, no conclusions regarding it's activity can be made and one would not conclude that it would

have practical utility as an immune stimulant. The Declaration of Dr. Fong is not specific to the protein, PRO335, of the instant application. The Declaration provides no data related to PRO335. Furthermore, the opinion of Dr. Fong that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12" is not supported by any facts or evidence of record. The references cited do not support this opinion and it is not clear how Dr. Fong arrived at this conclusion. There is no evidence of record which correlates an activity of at least 180% of control as predictive of an activity of IL-12 and there is no comparison of the claimed invention with IL-12. One of ordinary skill in the art would not conclude that PRO335 has the activity of IL-12 because there is absolutely no data provided to support such an assertion. Therefore, the Declaration is not persuasive to overcome the holding of a lack of patentable utility for the claimed invention based on the MLR assay.

Applicants argue, "Example 74 further explains that compounds which stimulate proliferation of lymphocytes in this assay "are useful therapeutically where enhancement of an immune response is beneficial." (page 208, lines 29-30). Accordingly, PRO335 has utility in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable." The questions are: What specific disease states would benefit by therapeutic enhancement of stimulation of lymphocyte proliferation by use of the claimed PRO335? What do the results of the MLR assay of Example 74, using PRO335, disclose about the disease state that could be treated by stimulation of lymphocyte proliferation? As disclosed by the examples provided in applicants' arguments different compounds effect the stimulation of lymphocyte proliferation to different degrees and in turn have different therapeutic effects on a diverse list of diseases. Il-2 arguments natural killer cell activity in patients with AIDS and is recommended for advanced renal cell carcinoma. Il-15 which was found to be at least as potent and effective as IL-2 in the MLR assay prolongs survival of lymphoma-bearing mice and suppresses pulmonary metastases induced by injection of sarcoma. Il-21 found to enhance the proliferation of T cells in an MLR assay potentially inhibits B16 melanoma tumors. Alpha-GalCer demonstrated to enhance the

T-cell response in an MLR assay inhibits tumor metastasis in liver or lung. Therefore, based on the varied effects of the compounds that have stimulated the lymphocyte proliferation assay no prediction as to the specific therapeutic value of PRO335 cannot be made without further experimentation. The compounds that tested positive in the MLR assays discussed above did not produce the same amount of stimulation in the assays and did not result as therapeutics for the same disease states.

Appellant's arguments directed to use of the MLR to evaluate compounds for use as immunomodulators is noted. However, in view of the Examiner's concession that the MLR is an art-accepted assay for this purpose, these arguments are moot.

Appellant cites case law concerning the Examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be considered. Applicant also points to the utility guidelines as directing the Examiner to accept an opinion from an expert. Appellant points to the statement in the Fong declaration that it is Dr. Fong's considered scientific opinion that "a PRO polypeptide shown to stimulate T-cell proliferation in the MLR assay of the present invention with an activity of at least 180% of the control is expected to have the type of activity as that exhibited by IL-12, and would therefore find practical utility as an immune stimulant". Applicants argue that barring evidence to the contrary regarding the above statement in the Fong declaration, this rejection is improper under both the case law and the Utility guidelines. This has been fully considered but is not found to be persuasive.

As discussed above, in assessing the weight to be given expert testimony, the Examiner may properly consider, among other things, (1) the nature of the fact sought to be established (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not Example 74 of the specification demonstrates that the PRO335 would be useful for therapeutic enhancement of an immune response. (2) The art provides support that the results of the MLR assay are generally predictive of in vivo effects (Haskill et al.), but the art also teaches that proper controls are required for meaningful results. These controls appear to be lacking in the instant application.

Additionally, the standard used in the specification (positive increases above control are considered positive) would not be accepted by those in the art as indicating that the claimed invention would have therapeutic value for enhancing an immune response. The art to which the invention pertains is immunology and the art accepted standard for determining biological activity is statistical significance. This standard is clearly evidenced by the references cited by Applicants and Examiner in that the data presented in these references are given with statistical analysis and conclusions drawn from the statistical significance of the results. Since no values are provided in the instant application, statistical significance cannot be ascertained. (3) Dr. Fong has an interest in the case since he is employed by the assignee. Finally, (4) while Dr. Fong bases his findings with reference to facts, the conclusions arrived at are not supported by those facts. For example, there is no evidence that the PRO335, has an activity of at least 180% in the MLR assay. Additionally, the references reviewed by Dr. Fong (Guber et al., Peterson et al., and Thurner et al.) are directed to IL-12, and not to the PRO335 of the instant application. None of the references indicate that an activity of at least 180% in an MLR is indicative of a protein having the type of activity as that exhibited by IL-12. In fact, none of the references use the results of the MLR for IL-12 to make predictions about the biological activities of any other compounds. The asserted correlation of an activity of at least 180% in an MLR with the biological activity of IL-12 is not supported by any evidence of record, and appears to be solely the opinion of Dr. Fong. Based on the totality of the evidence, considering it anew, it is maintained that one skilled in the art would view the MLR assay of Example 74 as merely preliminary with regard to whether or not PRO335 would be useful for therapeutic enhancement of an immune response. Further research would have to be done in order to determine if PRO335 stimulates proliferation of T-lymphocytes and, if so, whether or not the stimulation is significant enough to reasonably confirm the usefulness of PRO335 protein for therapeutic enhancement of an immune response. Thus, the specification does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

In conclusion the specification and applicants' arguments generally assert that the disclosed PRO335, based on the MLR reaction, stimulates proliferation of lymphocytes and is useful therapeutically where enhancement of an immune response is beneficial; however, this asserted use does not meet the three-pronged requirement of 35 U.S.C. 101 regarding utility, namely, that the asserted utility be credible, specific and substantial. Therefore, PRO335 polypeptide and the nucleic acid encoding PRO335 polypeptide do not have any specific and substantial utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

5. Claims 39-47 and 49-51 remain rejected under 35 U.S.C. 1 12, first paragraph for reasons of record.

Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

6. Claims 39-47 and 49-51 remain under 35 U.S.C. 112, first paragraph, as lacking enablement for reasons of record and those given below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue compounds which inhibit proliferation of lymphocytes are useful therapeutically where suppression of an immune response is beneficial. However, the ability of the claimed protein to stimulate or inhibit lymphocyte proliferation in the MLR assay does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function for a therapeutic suppression of the immune system. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be

beneficial is not enabled by the disclosure of the instant specification. The only use contemplated for the claimed invention is a therapeutic suppression of the immune system. Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result *in vitro* does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, while the art recognizes the MLR assay as accepted for screening for immunosuppressive molecules in vitro with a general, which is art recognized for being generally predictive of their in vivo effectiveness, this biological activity does not correlate to use of the claimed protein in a therapeutically effective manner, as the asserted use of the claimed invention proposes.

The questions are: What specific disease states would benefit by therapeutic enhancement of stimulation of lymphocyte proliferation by use of the claimed PRO335? What do the results of the MLR assay of Example 74, using PRO335, disclose about the disease state that could be treated by stimulation of lymphocyte proliferation? As disclosed by the examples provided by applicant different compounds effect the stimulation of lymphocyte proliferation to different degrees and in turn have different therapeutic effects. Il-2 arguments natural killer cell activity in patients with AIDS and is recommended for advanced renal cell carcinoma. Il-15 which was found to be at least as potent and effective as IL-2 in the MLR assay prolongs survival of lymphoma-bearing mice and suppresses pulmonary metastases induced by injection of sarcoma. Il-21 found to enhance the proliferation of T cells in an MLR assay potentially inhibits B16 melanoma tumors. Alpha-GalCer demonstrated to enhance the T-cell response in an MLR assay inhibits tumor metastasis in liver or lung. Therefore, based on the varied

effects of the compounds that have stimulated the lymphocyte proliferation assay no prediction as to the specific therapeutic value of PRO335 cannot be made without further experimentation. The compounds that tested positive in the MLR assays discussed above did not produce the same amount of stimulation in the assays and did not result as therapeutics for the same disease states.

The MLR assay is an accepted *in vitro* model for screening immunosuppressive agents for use in the prevention of graft-versus-host disease and graft rejection. However, the assay must be evaluated as it pertains to the asserted use of the claimed invention, which is for therapeutic enhancement of the immune response of an individual. If the claimed invention is to be used for therapeutic enhancement of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? Fung-Leung et al. cited by Applicants (see IDS 10/30/06) for support that the MLR assay is used for identifying immunomodulatory compounds. However, the disclosure of Fung-Leung et al. is much more than what is in the instant specification and the immunosuppressive effect being measured was specifically for alloantigens. Several controls were run, as were determinations that the inhibitory effect was not related to cell toxicity. Lastly, Fung-Leung et al. concluded that the results of the multiple MLR assays and controls "suggests its potential use as an immunosuppressant in clinical therapy" (page 364, first sentence). It was not until the compound was tested in an *in vivo* mouse model that the authors declared it an immunosuppressant. Therefore, the conclusions reached by Fung-Leung et al. are based on much more experimental data, assays and testing that that provided in the instant specification and the reference does not support the position that the MLR assay in the instant specification is predictive of use as a therapeutic compound for suppressing the immune response. The results of the MLR assay in the instant specification are merely preliminary, and much more experimentation is necessary for one of ordinary skill in the art to use the claimed invention in the manner disclosed. This experimentation would be considered undue, because until it is performed, the skilled artisan cannot use the claimed invention in the manner disclosed.

Further, no "particular antigen" is identified in the specification; there is no guidance as to how PRO335 could be used to boost the response to any antigen. Current Protocols in Immunology states on p. 3.12.11 that the MLR "only detects dividing cells instead of measuring true effector T-cell function" and that it is "not clear which T cell function is measured in proliferate assays", and further that "the proliferate response should be used solely as a general indicators of T cell reactivity". Data obtained might variously reflect proliferation of CTL, lymphokine producing T cells, or non-activated bystander cells and will be severely affected by the function of non-T cells. Differences in responsiveness in a proliferative assay in part reflect differences in IL-2 production, according to Current Protocols in Immunology. As has been stated previously, the MLR measures the reactivity of one individual to another and is, as Current Protocols in Immunology states, highly variable. Current Protocols in Immunology in fact describes many variables that must be controlled for. In the instant application, no such controls, such as for maximum response or for the inherent variability of individual responses, are provided. There is no indication of the statistical significance of the results. There are no autologous controls. No correlation is provided to any particular *in vivo* function; there is no guidance to indicate that PRO335 could be used to any therapeutic effect for the treatment of diseases such as cancer or HIV. The references cited by Applicant fail to provide compensatory guidance. Steinman and Thurner et al. (cited by applicants on 10/25/04) address the utility of dendritic cells but not of a stimulatory MLR. Gubler (cited by applicants on 10/25/04) describes the identification of the molecule IL-12 but uses the MLR merely to compare activities, not as the basis for describing a molecule as a therapeutically useful immunostimulant. The subsequent research of Peterson et al. (cited by applicants on 10/25/04) was clearly required to suggest that the molecule could be used in this fashion. Thus, without further guidance correlating the observed stimulatory activity to a particular, useful property, it would require undue experimentation to use PRO335.

Because the claimed invention is not enabled and does not meet the requirements of 112/1st paragraph for the reasons provided above and the previous office actions.

7. Claims 39-43, 50 and 51 are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant ad that the inventors), at the time the application was filed, had possession of the claimed invention. The claims are drawn to polypeptide having at least 80%, 85%, 90%, 95% or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polynucleotide or encoded polypeptide possess a specific function associated with PRO335, only that the polypeptide encoded by said polynucleotide be immunostimulant. All polypeptides can be considered immunostimulants. Apart from the polynucleotide of SEQ ID NO:289 encoding the polypeptide of SEQ ID NO:290, the particular conserved structures or other distinguishing structural features critical for a specific activity of PRO 335 are not disclosed. Thus, the claims are drawn to genus of polypeptides that is defined only by sequence identity and general activity (applicable to many other polynucleotides) and no specific activity that can be associated with any specific domains of PRO335.

Applicants argue and state, "the specification shows that Applicants were in possession of the invention as of the effective filing date of an application is a factual determination, reached by the consideration of a number of factors, including the level of knowledge and skill in the art, and the teachings provided by the specification. The inventor is not required to describe every single detail of his invention. An applicant's disclosure obligation varies according to the art to which the invention pertains." Applicants further argue that structure and function of the claimed variants can be determined based on the specification. Applicants' arguments have been fully considered but they are not found persuasive.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor

present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved for function. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a polypeptide, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the polypeptide has been isolated. Thus, claiming all polypeptides that achieves a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. The claims recite a broad arbitrary structural relationship between the claimed polypeptides sequences, either in terms of its nucleotide sequence of PRO335 or the polypeptide encoded, and the single disclosed species of nucleotide sequence and amino acid sequence, respectively. The claims are not even directed to polypeptides, which have a specific function associated with PRO335, only a general function associated with all proteins. Further, if applicant argues PRO335 works in the MLR assay by immumostimulation, it must be noted that the immunostimulation activity is not considered an activity that that has been correlated with a specific structure contained in PRO335 as it pertains to said assay. Further non-functional or functionally unrelated proteins to PRO335 are encompassed by the claims. The recited structural relationships are arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at either the nucleotide or amino acid level; and the specification does not describe a single species of polypeptide that is a functional protein that is not 100% identical to the recited polypeptide, or encoded by a nucleic acid that is not 100% identical to SEQ ID NO:289.

While one of skill in the art can readily envision numerable species of polypeptide sequences that are at least a given % identity to a reference polypeptide, one cannot

envision which of these polypeptides has a specific activity of the protein of SEQ ID NO:290. The fact remains that the actual amino acid sequences of such a polypeptide *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences to all possible sequences with an arbitrary structural relationship with a known functional sequence. For example, if one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 90% identity to the reference amino acid sequence, he would be no more able to say whether it encoded a functional polypeptide than if the nucleotide sequence encoded a polypeptide that was only 10% identical to the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

To put the situation in perspective, the number of possible amino acid sequences of 100 amino acids in length is 20^{100} (approx. 10^{130}) and the number of possible nucleotide sequences of 300 nucleotides in length is 4^{300} (approx. 4×10^{180}) . The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! + X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be inserted, deleted or substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids).

For a 100 amino acid sequence that is at least 90% identical to a reference sequence of 100 amino acids, the number of possible sequences having 9 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 6×10^{23}. Whereas the number of possible sequences having 10 amino acid substitutions relative to the reference (the final term of the formula) is

approximately 1.1 x 10^{26}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. It can also be shown that N can be approximated by the formula $X^nL^n/n!$, where n<<L. Using this formula to approximate N in this example gives a value of 1.7 x 10^{26}. For a 300 nucleotide reference sequence, the number of possible 300 nucleotide sequences that are at least 90% identical to the reference is approximately 1.6 x 10^{56}.

In the present case, the reference amino acid sequence, SEQ ID NO:290 is 1059 amino acids long, and the reference nucleotide sequence, SEQ ID NO:289 is 3662 nucleotides long. Using the approximation formula, the number of possible amino acid sequences and nucleotide sequences that are at least e.g. 80% identical to the reference amino acid sequence or nucleotide sequence, would be much larger than 6 x 10^{23} and 1.6 x 10^{56}, respectively. While limiting the scope of potential sequences to those that are at least e.g. 80% identical to a reference greatly reduces the number of potential sequences to test, it does not do so in any meaningful way. All of these values greatly exceed the estimated number of atoms in the universe (10^{70} to 10^{90}). Thus, limiting the claims by the recited structural relationships merely reduces the degree of impossibility of making and testing sequences for those, which encode a functional protein encompassed by the claims. Therefore, inclusion of the structural relationships in the claim does not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.*

The specification does not provide any information on what amino acid residues are necessary and sufficient for a functional activity. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in an active PRO335 polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there are no other examples of proteins that have structural homology with SEQ ID NO:335 to predict function or functional domains required for activity, it is not possible to even guess at the amino acid residues, which are critical to its structure or function based on sequence conservation. Therefore one cannot predict variant amino acid sequences for a

biologically active polypeptide. Rather one must engage in case to case painstaking experimental study to determine active PRO335 variants. Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a biologically active PRO335 with an amino acid sequence differing from SEQ ID NO:290 since the amino acid sequence of such polypeptides could not be predicted.

The specification discloses only one putative amino acid sequences, SEQ ID NO:290, for a polypeptide having the necessary properties for the disclosed uses, and provides no guidance on obtaining functional polypeptide variants of SEQ ID NO:290 encoded by the nucleic acid of SEQ ID NO:289, which would be suitable.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 , clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description" inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the ad to recognize that (he or she) invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird,* 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF'S were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polynucleotides encoding polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 290 but not the full breadth of the claims meets the written description provision of 35 U.S.C.112, first paragraph. Applicant is

reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1 115).

8. No claim is allowed.

9. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Nirmal S. Basi NSB
Art Unit 1646
1/21/07

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